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14. ABSTRACT

Organophosphate (OP) poisoning can result in status epilepticus (SE), which can become pharmacoresistant if treatment is delayed. Virtually no data exist on OP-induced SE in immature animals, even though the immature brain is likely to respond differently to OPs, and the optimal therapies are also likely to differ from adults. Our aim is to identify novel drugs that block pharmacoresistant OP-induced SE, as well as pharmacoresistant LiPilo-induced SE, in immature rats, which would thus be candidate therapies in children. As a collaborative program over the past 2 years, we have provided USAMRICD investigators with our novel miniature telemetry devices and recording apparatus for recording from postnatal day 7 (P7) and P14 rats. We have developed rat models for both diisopropylfluorophosphate (DFP) and LiPilo exposure for ages P7, P14, P21, and P28. Surprisingly, so far, P7 and P14 rat pups have only generated brief (i.e., minutes) periods of seizure behavior in response to DFP and LiPilo, while P21 and P28 animals develop robust SE that lasts for several hours. We have observed extensive neuronal injury in P28 and P21 rats using Fluoro-Jade B as a marker. We have characterized the effects of midazolam and diazepam on DFP-induced SE in P21 rat pups, and we found that midazolam ameliorates the SE and the neuronal damage triggered by the OP. Diazepam had similar properties, but at the dose tested, was not as effective as midazolam. We have developed and characterized a model for acute DFP and LiPilo inducedt SE that is now ready for testing reference and investigational anti-seizure drugs in P21 and P28 rats. Further experiments are needed to characterize models of P7 and P14 DFP-induced SE.

15. SUBJECT TERMS
Status Epilepticus, seizure, organophosphate, DFP, pediatric, neuronal injury, anticonvulsant, midazolam

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Introduction

Organophosphate (OP) exposure can lead to continuous, repetitive seizures (i.e., status epilepticus, SE), which are associated with high morbidity and mortality and can become pharmacoresistant. Very little has been described of the seizure generating effects of OPs in a pediatric model, and no studies examine the efficacy of anticonvulsants in OP-induced SE in immature animals. Our aim is to develop a model of pediatric OP exposure resulting in SE, with the ultimate goal of identifying novel drugs that block pharmacoresistant OP-induced SE in children.

EEG monitoring involved a novel miniature telemetry device, which has allowed us to study freely-moving rats, thus leading to unrestricted behavior. Neuropathological data were analyzed with FluoroJade B, a marker for dying neurons. Pharmacological agents that were to be tested were diazepam, midazolam, phenobarbital, fos-phenytoin, and propofol.

The “Statement of Work” – slightly modified in response to NINDS CounterACT and USAMRICD - was:

1. Provide USAMRICD researchers miniature telemetry systems and the know-how necessary to record EEG from immature rats for the nerve agent experiments at USAMRICD
2. Develop animal models of nerve agent exposure in immature (post-natal days 7, 14, 21, and 28) rats using seizure models based on the administration of Li-pilocarpine and particularly the OP, diisopropylfluorophosphate (DFP), to record electrographic SE. Characterize the electrographic characteristics of these seizures and determine the neuropathological effects of these seizures in various brain areas.
3. Once these models have been developed and characterized, cross-validate the anticonvulsant and neuroprotective properties of up to five FDA-approved or investigational drugs in these models. The drugs initially proposed for testing were diazepam, midazolam, phenobarbital, fosphenytoin, and propofol.

Body

1. **Provide USAMRICD researchers telemetry devices and the apparatus and know-how necessary to record EEG from immature rats for the nerve agent experiments at USAMRICD**

Investigators at the USAMRICD were provided with miniature telemetry devices and recording apparatus for examining EEG in neonatal and juvenile rats. Dr. Mark Lehmkuhle provided information and assistance on implementation of the transmitter devices and the overall recording system.

2. **Develop animal models of nerve agent exposure in immature (post-natal days 7, 14, 21, and 28) rats using Li-pilocarpine and the OP, DFP, seizure models to record electrographic SE. Characterize the electrographic characteristics of these seizures and determine the neuropathological effects of these seizures in various brain areas.**

Characterization of the behavioral effects of DFP.

Animals of all ages showed the following toxic signs in their behavioral response to DFP: head-bobbing, whole-body tremor, myoclonic jerks, gasping, urination, defecation, excessive salivation, and Straub tail. Piloerection, hyper-lacrimation and exopthalmos were observed in P21 and P28 rats. Vocalizations were audible at P7 and P14. Due to the immature limb development at P7, whole body arching was observed only at this age. Similarly, swimming motions of the limbs were seen only in P7 pups. In general, the younger the animal, the more quickly the animal appeared to recover from the toxicicity. Also, mortality was most often observed within the first 10-15 min after DFP administration, most likely due to the central suppression of respiration. Li-pilocarpine resulted in the same behaviors, but also included forelimb clonus, rearing, and falling that is associated with Racine scale seizures 3-5 (Racine, 1972).

Electrographic effects of DFP as a function of age

As illustrated in Table 1, behavioral seizures in P28 rats, defined generally as whole body tremors, were observed at the lowest dose of DFP (3 mg/kg). However, electrographic SE was not observed with subdural recording until 4 mg/kg, and a higher rate of occurrence of electrographic SE was observed at 5.5 mg/kg DFP. No behavioral correlates corresponded to electrographic SE. With Li-pilocarpine treatment, however, behavioral correlates paralleled the electrographic SE (Scholl, et al., 2013). Intracerebral recordings of local field potentials are needed to confirm that those events that appear to be behavioral seizures in DFP-treated rats are actually associated with electrographic seizures. For DFP-treated animals, EEG recording was required to be sure of the occurrence of actual seizure activity.

DFP Dose (mg/kg)	Behavioral Seizures	SE	Mortality
3.0 (n=3)	100%	0%	0%
4.0 (n=7)	100%	14%	0%
5.5 (n=4)	100%	75%	50%
6.0 (n=8)	100%	63%	25%
6.5 (n=12)	100%	25%	42%

Table 1. Summary of DFP dose-ranging studies in telemetry-implanted P28 rat pups.

Electrographic SE in P28 and P20/21 rats

Electrographic SE was studied in P28 (Fig. 1) and P20/21 rats(Fig. 2), as expected, SE consisted of robust, high-amplitude and high-frequency EEG activity, compared to the baseline prior to administration of DFP. Electrographic SE from DFP was compared LiPilo model (Fig. 3). When the gamma band of EEG activity was isolated and compared across groups of rats treated with DFP versus Li-Pilo, the variability and magnitude of the gamma power was greater in rat pups treated with LiPilo than with DFP (Fig. 4).

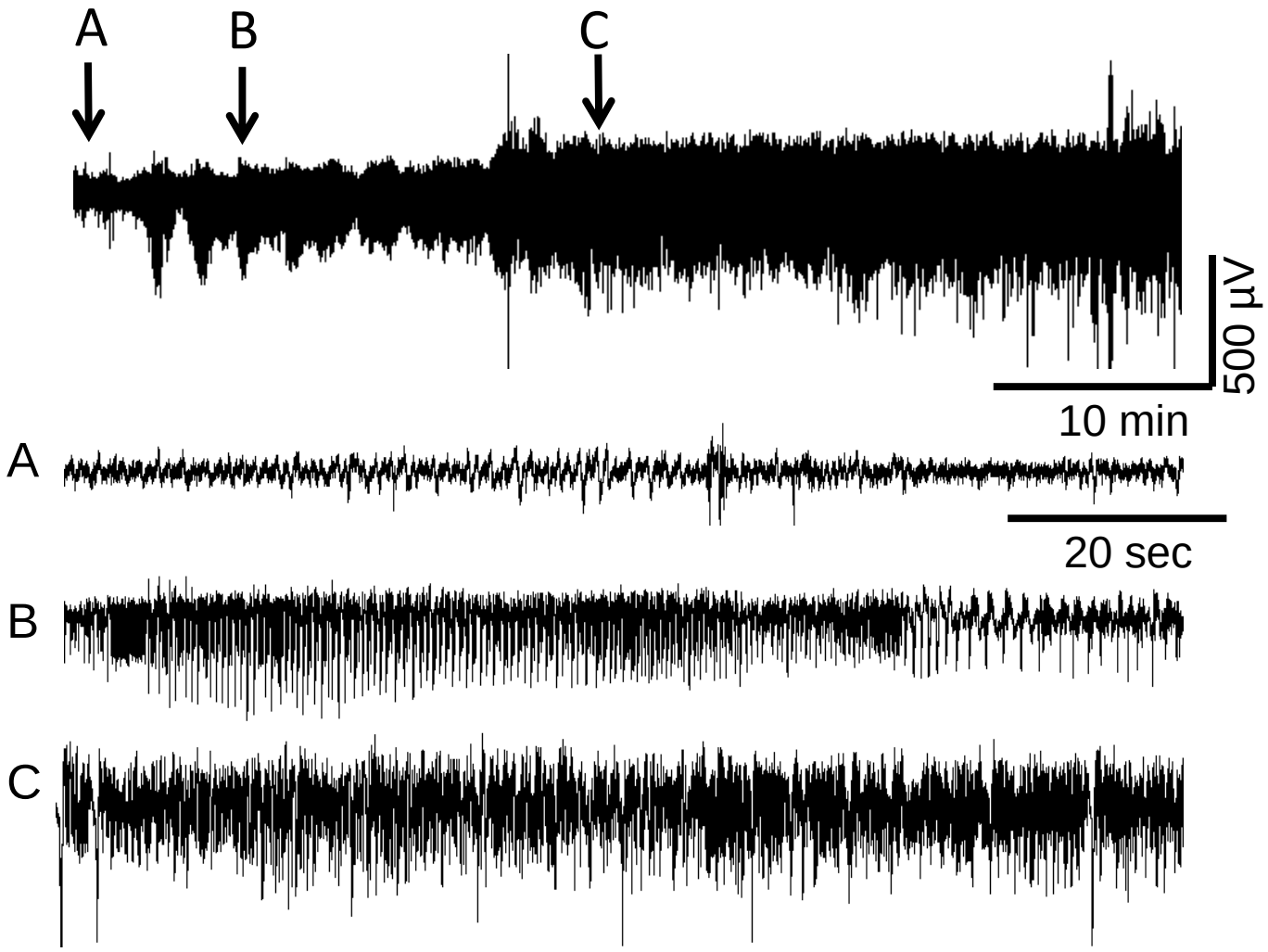

Figure 1. DFP-induced status epilepticus in a P28 rat. Animals were treated with 0.026 mg/kg pyridostigmine bromide (i.p.) 30 min prior to s.c. injection with 5.5 mg/kg DFP (s.c.). At 1 min after DFP administration, animals were given 0.1 mg/kg atropine sulfate admixed with 25 mg/kg 2-PAM (i.p.).

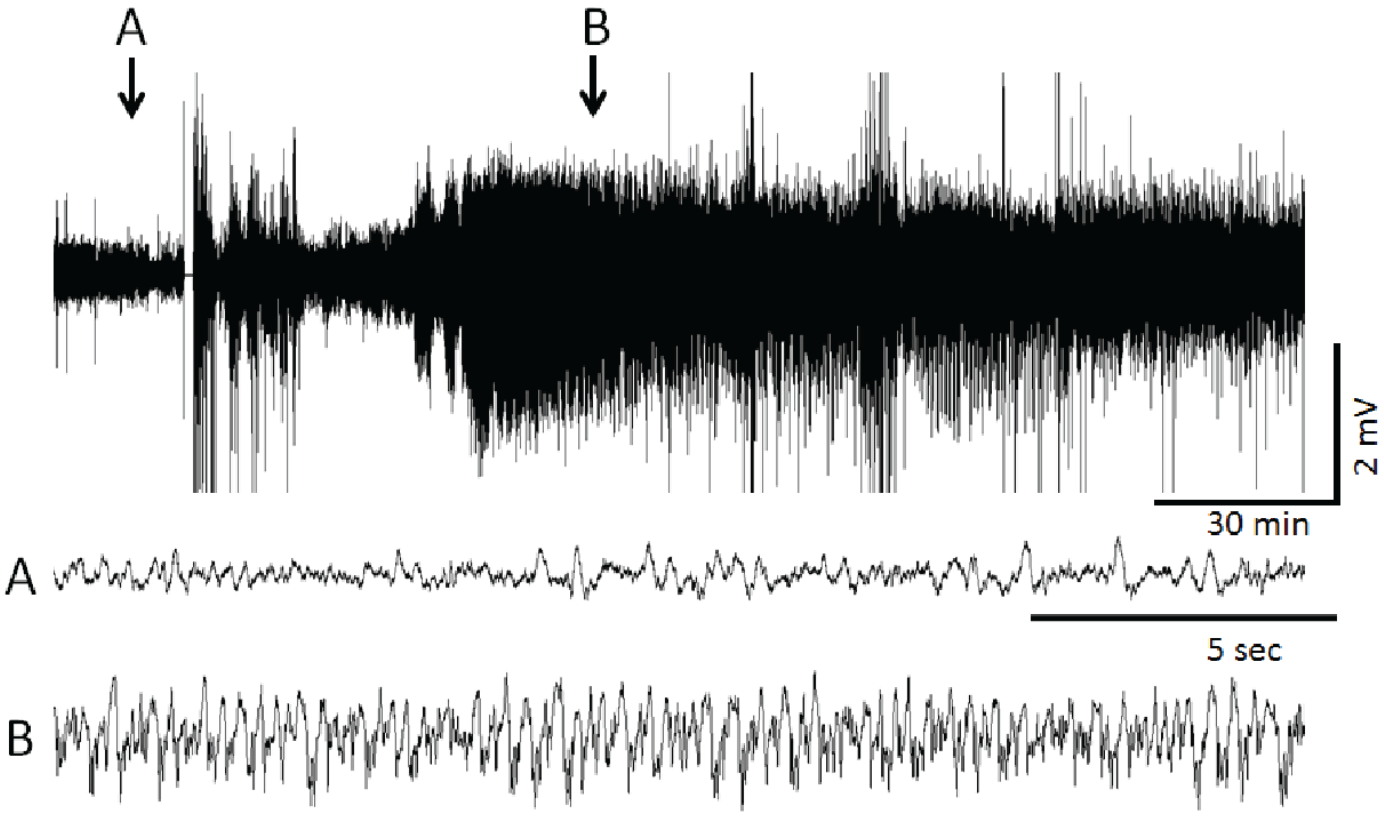

Figure 2. Electrographic SE recorded from DFP-treated P21 rat. Temporal expansion of the baseline before DFP administration (A) and after the onset of DFP-induced SE (B).

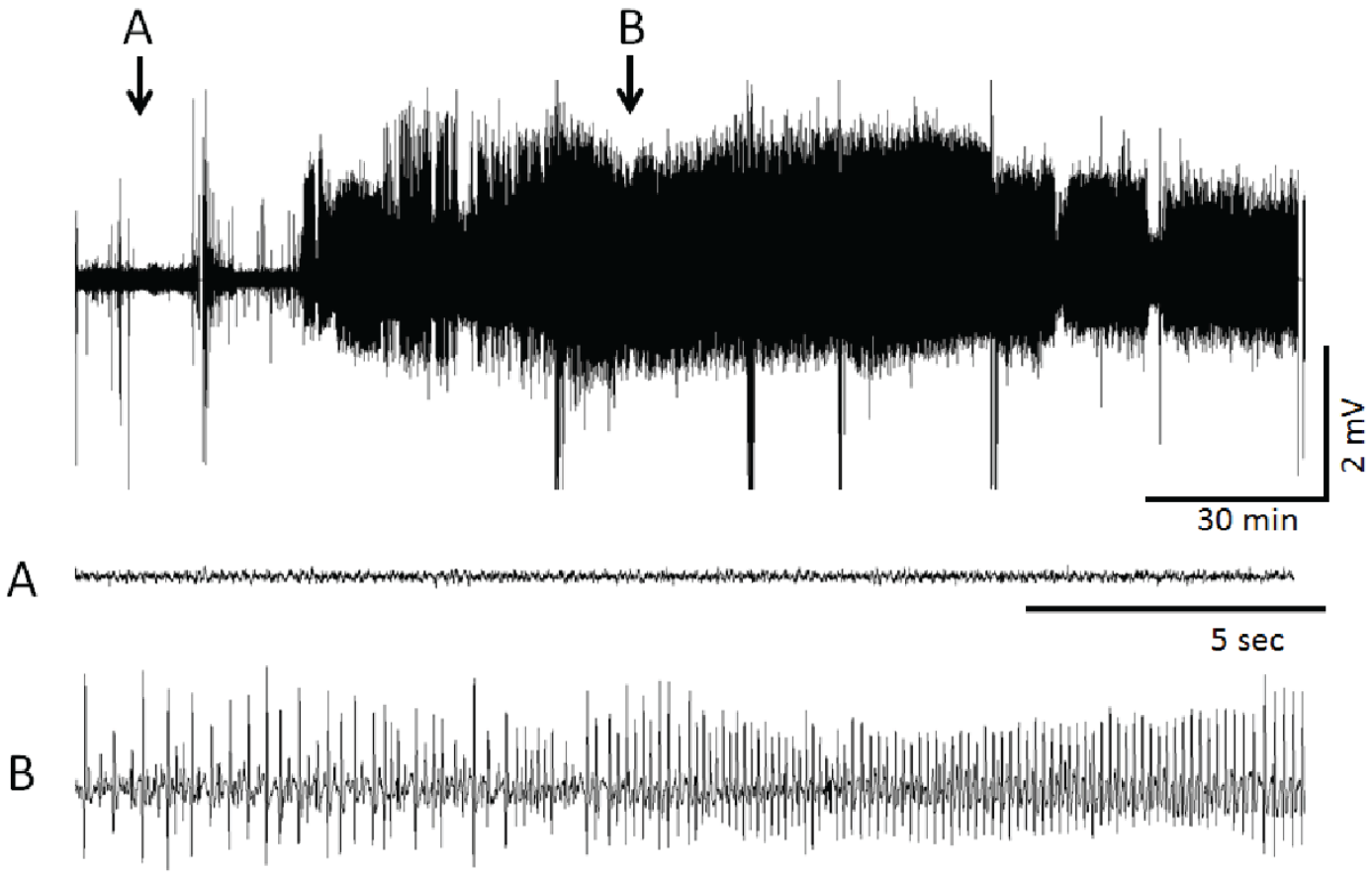

Figure 3. Li-Pilo treatment also elicited SE, and was compared to DFP-induced SE. Rats were treated with 127 mEq/kg of LiCl 16-18 hr prior to 50 mg/kg pilocarpine. Expansion of pre-pilocarpine baseline (A) and post-pilocarpine SE (B).

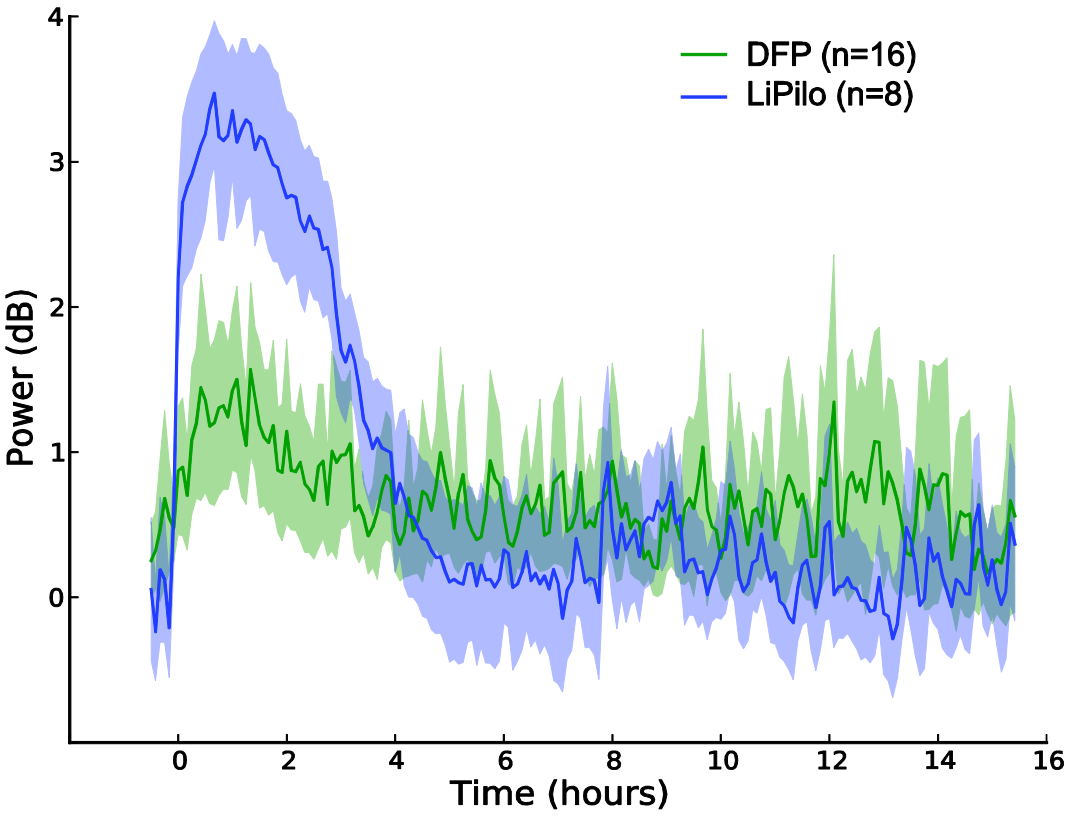

Figure 4. For P20/21 rat pups, the EEG was band-pass filtered to isolate the gamma band, which showed that the electrographic SE after DFP treatment (green) was less intense than after LiPilo (blue)

Electrographic seizures in P14 rat pups

In P14 rat pups treated with DFP, SE had a shorter duration compared to P28 and P21 (Fig. 5; compare with Figures 1 and 2). DFP-induced SE was compared to LiPilo-treated in P13/14 rat pups (Fig. 6). Figure 7 shows the temporal pattern of electrographic activity after DFP and LiPilo treatment, as analyzed with the mean coastline index of the EEG over time. With this analysis, LiPilo treatment in P13/14 rats caused electrographic SE that lasted longer than SE induced by DFP treatment.

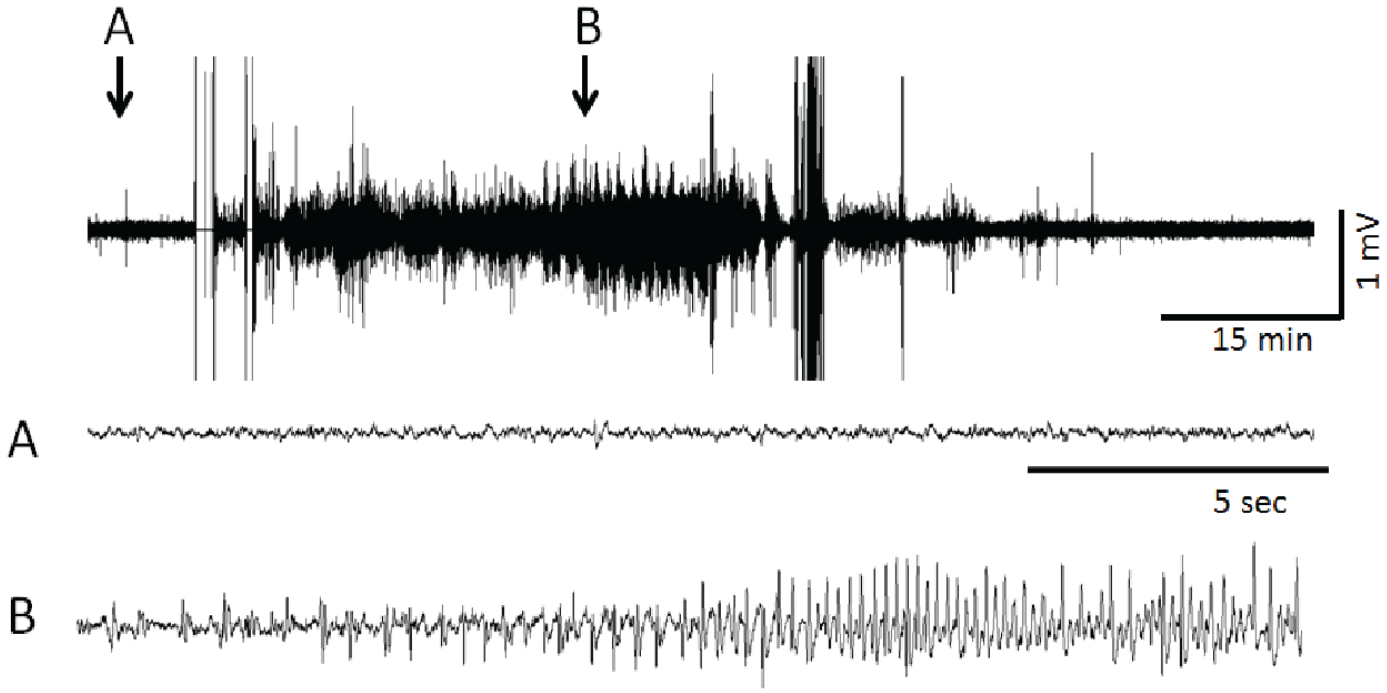

Figure 5. EEG of DFP-treated rat pups at P14. Before (A) and after DFP (B).

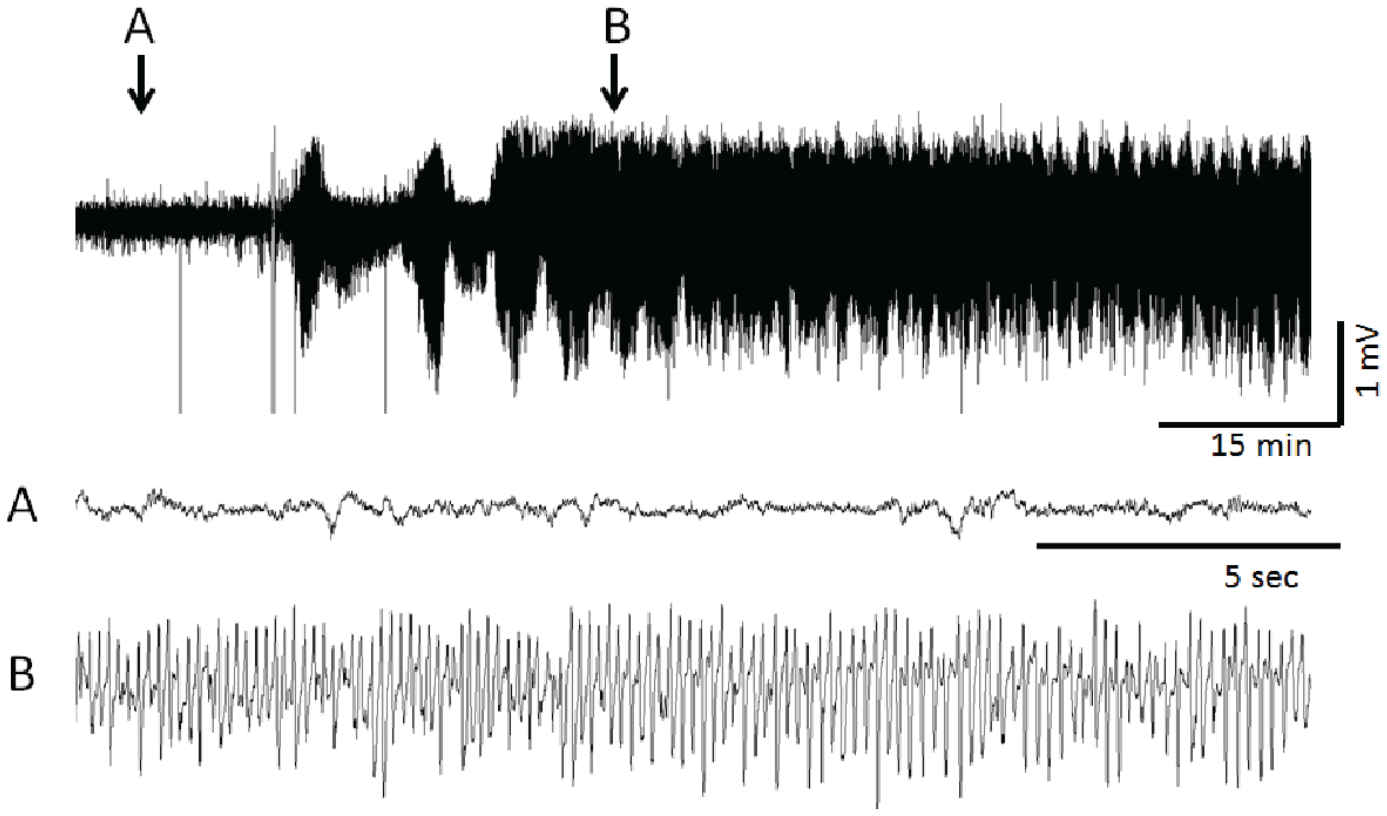

Figure 6. SE recorded from LiPilo-treated rats at P13/14. (A) Baseline obtained prior to SE, and (B) robust electrographic SE.

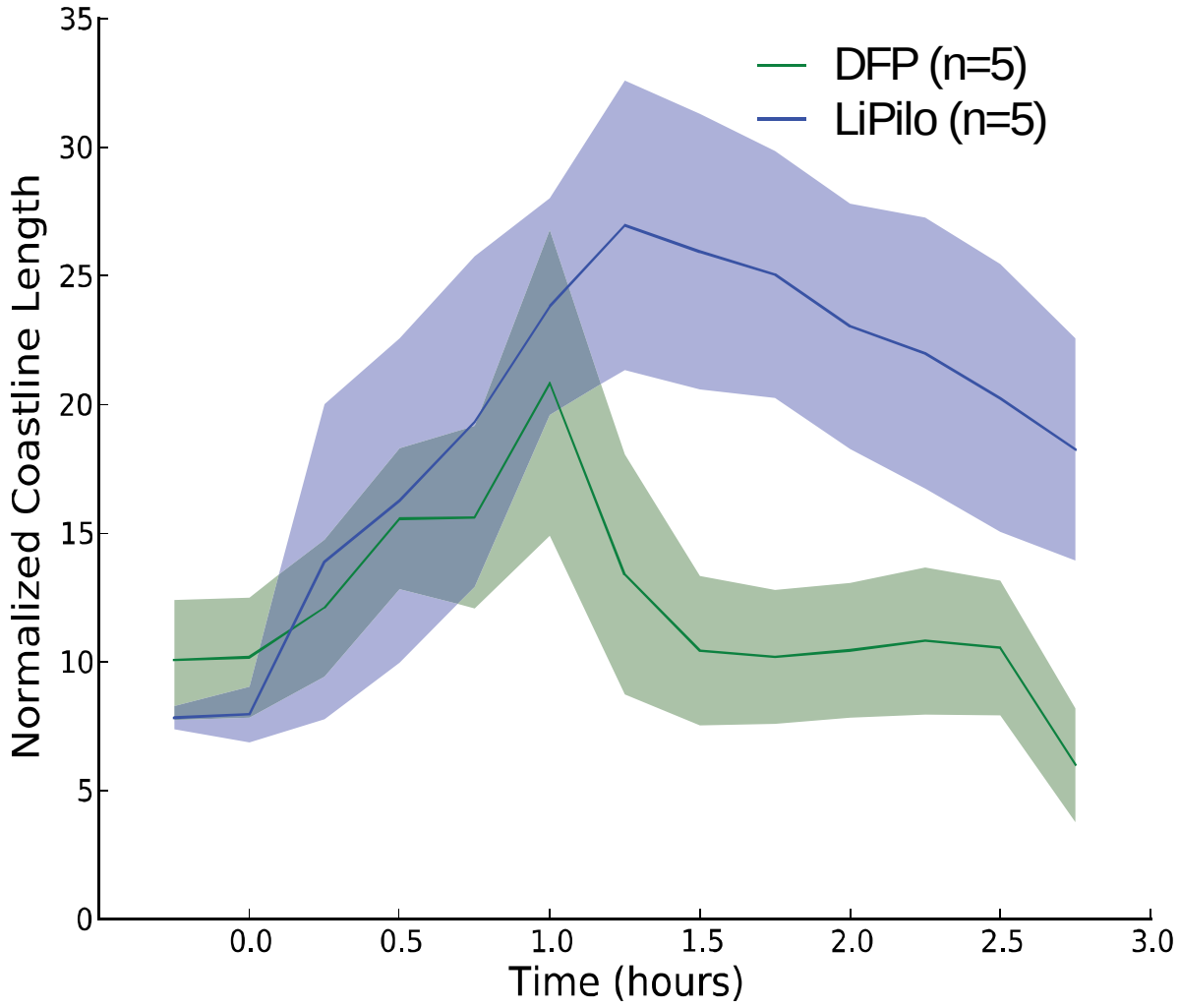

Figure 7. Mean coastline index for DFP- and LiPilo-treated rat pups at P13/14.

Rarity of electrographic seizures in DFP-treated rat pups at P7

The electrographic activity after DFP or LiPilo treatment at P7 differed from the activity elicited in the older rat pups (see above). In most cases, DFP administration did not evoke electrographic seizure activity (Figure 8); only bursts of spikes and/or spike-and-wave discharges were observed, and this activity only occurred intermittently. The electrographic SE seen in older rat pups was not observed at P7. Recognizable seizure activity (Fig. 9 and 10) was observed in only 3/33 (11%) of rats at P7, and those seizures did not occur until >2 hr after DFP administration. LiPilo-induced seizure activity occurred earlier after injection of Li-Pilo than for DFP (Fig. 10). Despite the differences between DFP- and LiPilo-induced seizure activity at P7, these differences were minor compared to the differences between P7 and the older animals after administration of DFP or LiPilo. The lack of robust SE at P7 and the rarity of repetitive seizures in rat pups was surprising, and suggested that hyper-excitation with these cholinergic convulsants does not lead sustained and prolonged periods of seizure activity at this age.

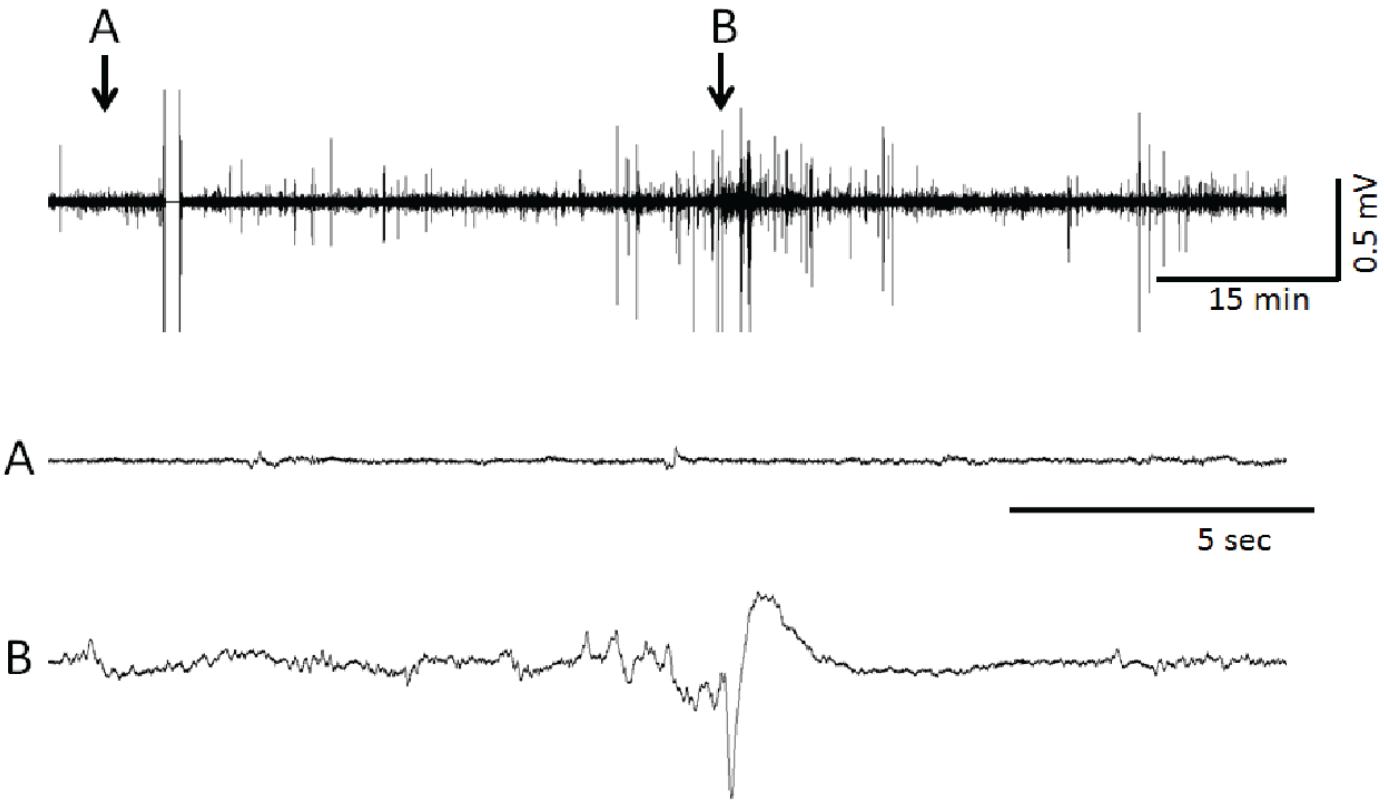

Figure 8. EEG record of P7 rat pups before (A) and after (B) DFP administration. Note the lack of robust seizure activity, and the relatively rare occurrence of spike-like events in the EEG.

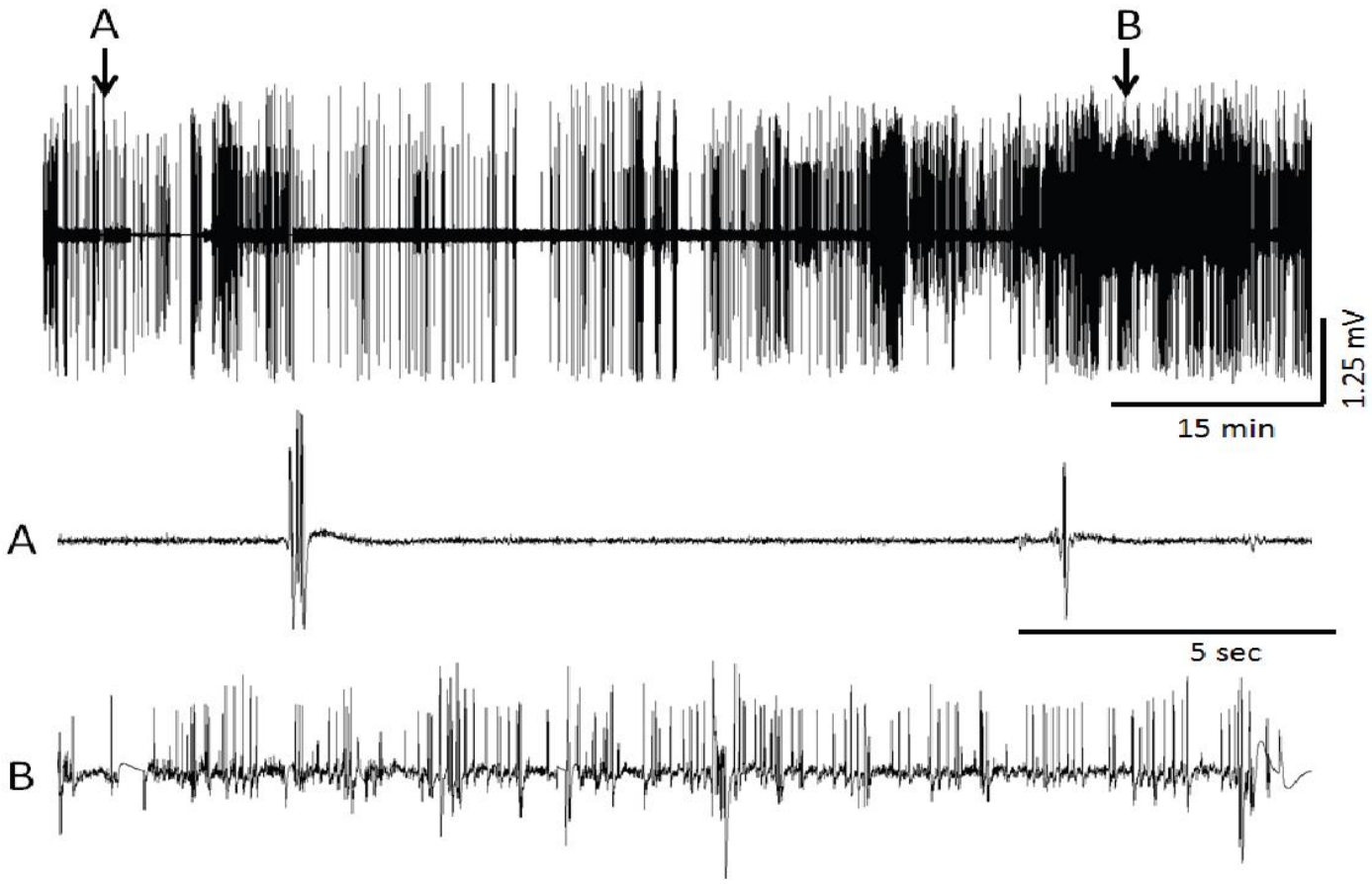

Figure 9. Seizure activity in a DFP treated P7 rat. Note that this type of repetitive seizure activity was extremely rare (11%). Before seizure activity (A), and during seizure activity (B).

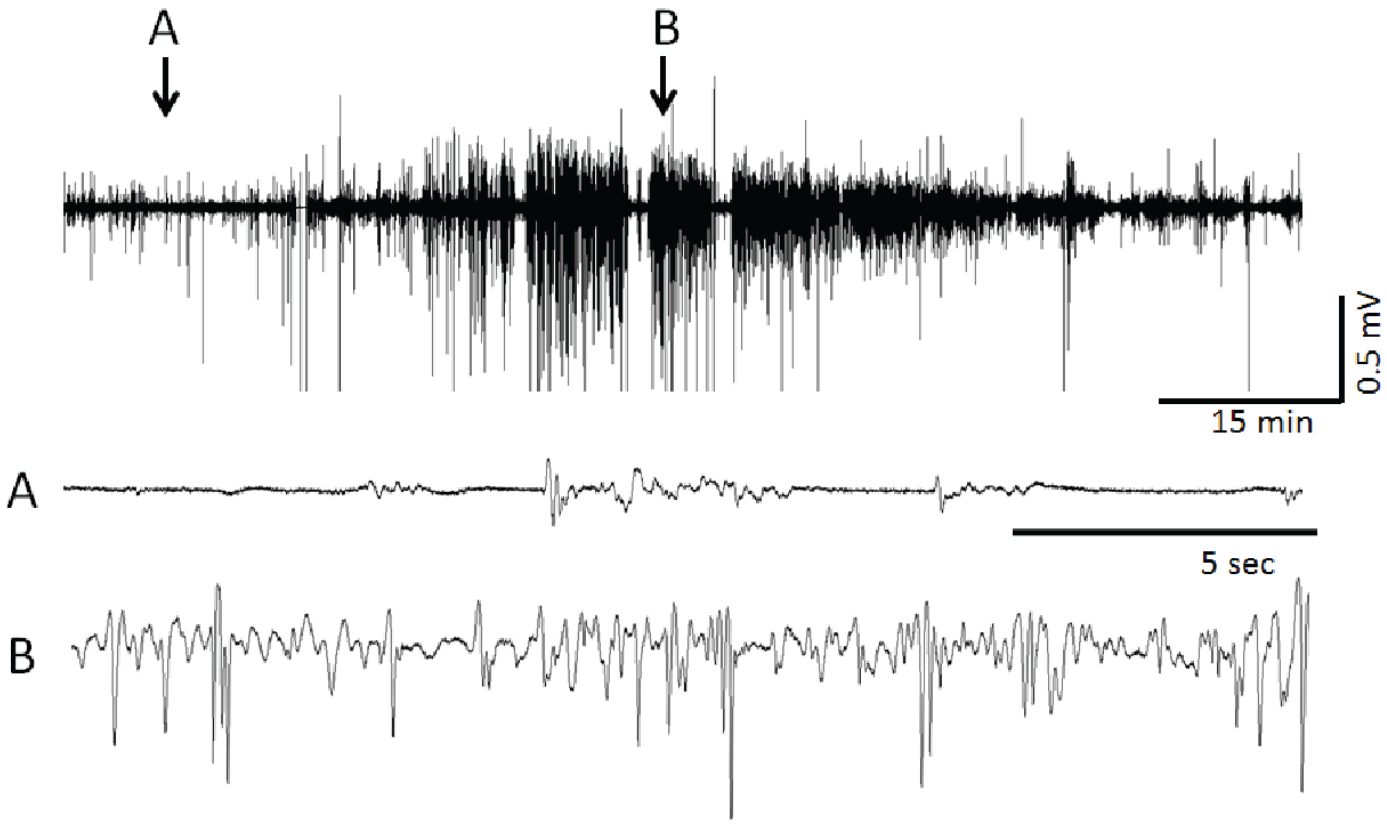

Figure 10. Electrographic seizure activity in a LiPilo treated P7 rat pup. Before pilocarpine (A) and after pilocarpine (B). Note that this type of repetitive seizure activity was rare at this age.

Characterization of the neuropathological effects of DFP

The brains of rat pups that were treated with DFP and that experienced both behavioral and electrographic seizures were sectioned and stained with Fluoro-Jade B (F-J B). Figure 11 shows representative sections from rat pups treated at P14, 21, and 28. The P14 animals (Fig. 11A) showed some damage in the thalamus and the amygdala, but P21 animals (Fig. 11B) showed greater damage and more widespread damage in these two structures, plus injury was also present in the hippocampus. The P28 rat pups exhibited extensive signs of neuronal injury (Fig. 11C) in more nuclei in the thalamus and amygdala, and F-J B was also observed in the hilus and neocortex. Control animals showed no F-J B staining (data not shown). The greater damage with increased age has been seen previously with Li-Pilo (Kubova et al., 2002; Priel et al., 1996). Figure 12 shows images of the heavy staining in DFP-treated rats at P28 for the dorsomedial amygdala (A), mediodorsal thalamic nuclei (B), dorsal CA1 region (C), and ventral CA1 region (D). In addition to the regions shown in Figure 12, the piriform cortex, endopiriform, and other thalamic nuclei were heavily stained. Lighter staining was observed in the neocortex and hypothalamus.

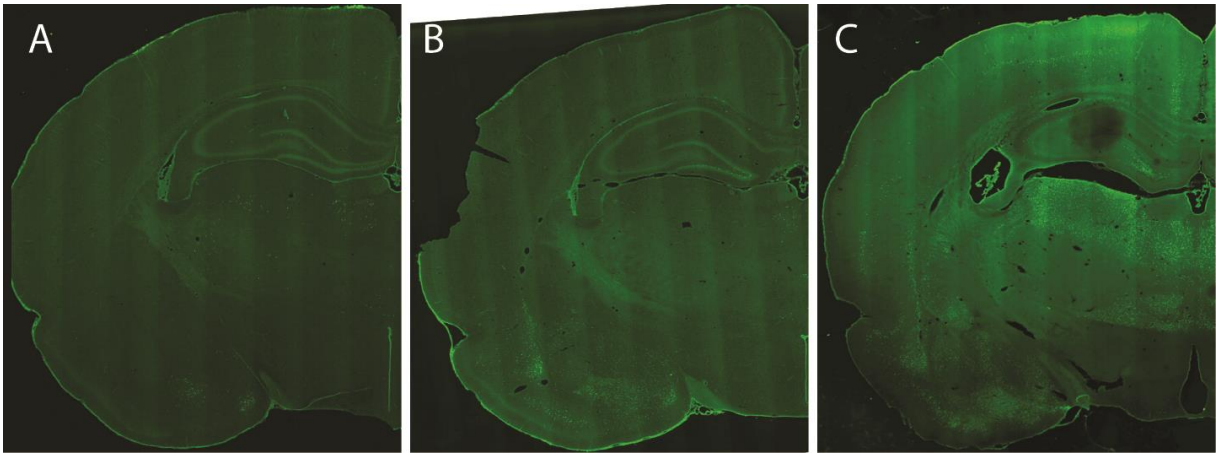

Figure 11. Representative coronal sections from P14 (A), P21 (B), and P28 (C) animals. Sections were taken from ~ -2.56 Bregma.

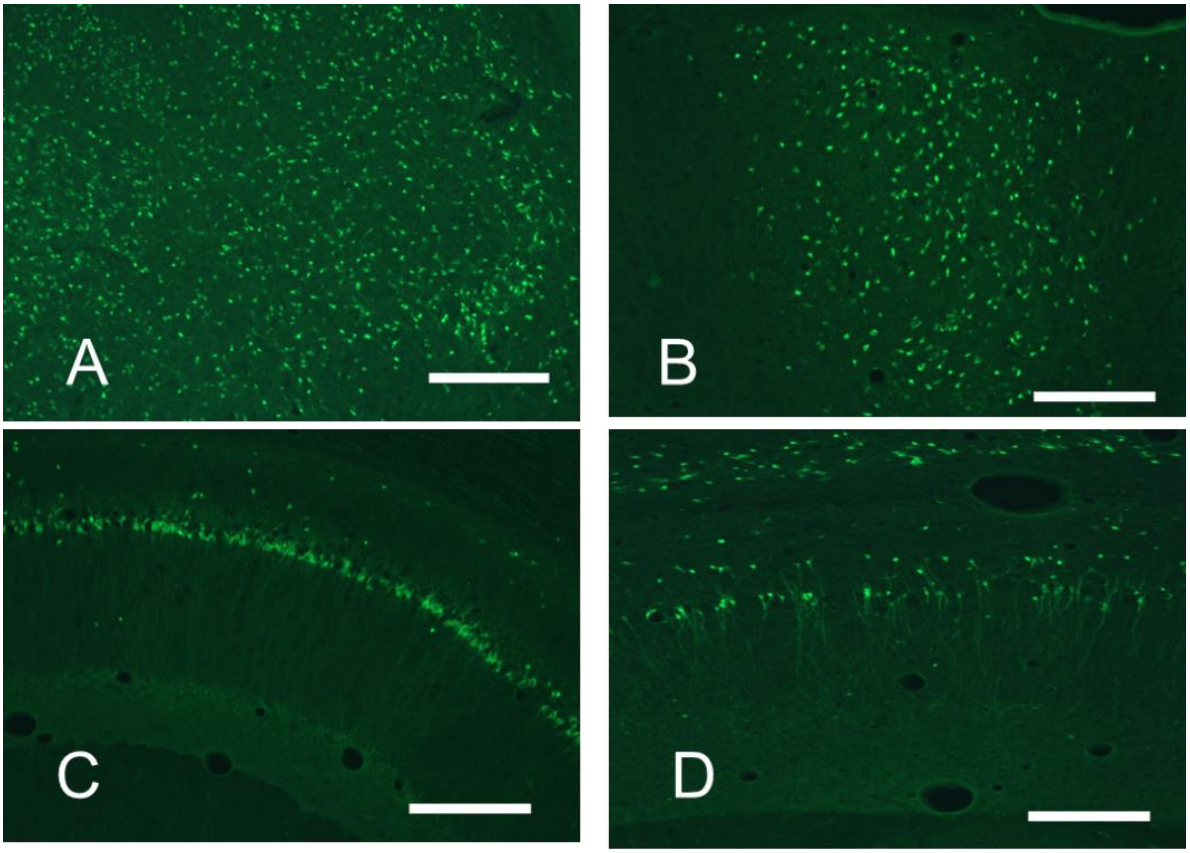

Figure 12. FluoroJade B staining of DFP-treated rats at P28. Representative images of the dorsomedial amygdala (A), mediodorsal thalamic nuclei (B), dorsal CA1 region (C), and ventral CA1 region (D). The calibration bar corresponds to 100 µm.

For comparison, F-J B staining after LiPilo treatment at P21 rat was robust in the hilus, amygdala and cortex (Fig. 13 A-C). At P21, F-J B staining after DFP treatment was usually absent in the cortex, but still robust in the hippocampus and amygdala (Fig. 13 D-F). The density of F-J B staining in these regions was quantified using a counting procedure similar that employed by Jiang and collaborators

(2013). Regions of interest were given a score of 0-3 based on the number of FJ-B-stained neurons present: 0 = 0-2 cells, 1 = 3-30 cells, 2 = 31-100 cells, and 3 = >101 cells. In general, neuronal injury was greater in the LiPilo-treated rat pups at P21 compared to those treated with DFP (Table 2).

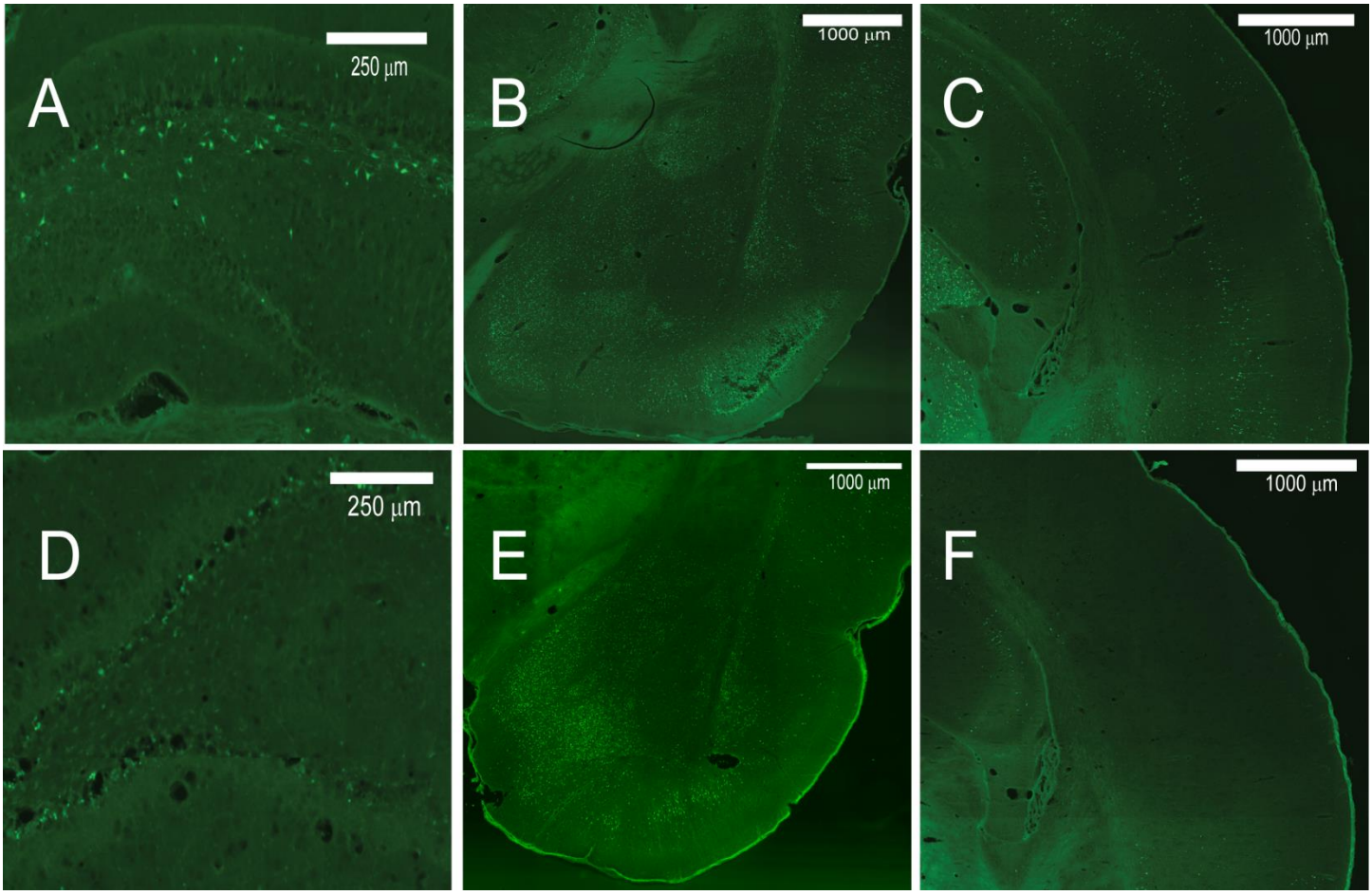

Figure 13. F-J B staining in LiPilo (A-C) or DFP (D-F) treated P21 rats. Hilus (A, D), amygdala (B, E) and parietal cortex (C, F)

	DFP	LiPilo
dCA1	2.21 ± 0.33	2.15 ± 0.24
dCA3	0.68 ± 0.11	1.31 ± 0.13**
Hilus	0.41 ± 0.13	1.29 ± 0.10**
DG	1.34 ± 0.25	1.86 ± 0.34
BA	2.22 ± 0.05	2.14 ± 0.12
LA	2.35 ± 0.09	2.33 ± 0.08
MD	2.57 ± 0.08	2.72 ± 0.07
Pir	2.89 ± 0.09	2.71 ± 0.10**
Par	0.79 ± 0.35	2.56 ± 0.12*
ENT	2.95 ± 0.04	2.82 ± 0.12
vCA1	2.21 ± 0.31	2.75 ± 0.25
vCA3	0.48 ± 0.10	2.22 ± 0.12***

Table 2. Neuronal injury assessed by F-J B staining in regions of interest in LiPilo and DFP treated P21 rats. Two-tailed t test with Mann-Whitney post-hoc test. *p < 0.05, **p < 0.01, ***p < 0.001.

3. **Once these models have been developed and characterized, cross-validate the anticonvulsant and neuroprotective properties of up to five FDA-approved or investigational drugs in these models. The drugs initially proposed for testing were diazepam, midazolam, phenobarbital, fosphenytoin, and propofol.**

Effects of midazolam on electrographic activity

We have begun analyzing anticonvulsants in P21 and P28 animals. Figure 14 shows an EEG trace of SE from a P21 animal, and the effects of 2 mg/kg midazolam given 1 hr after DFP injection. Midazolam halted both behavioral and electrographic seizures.

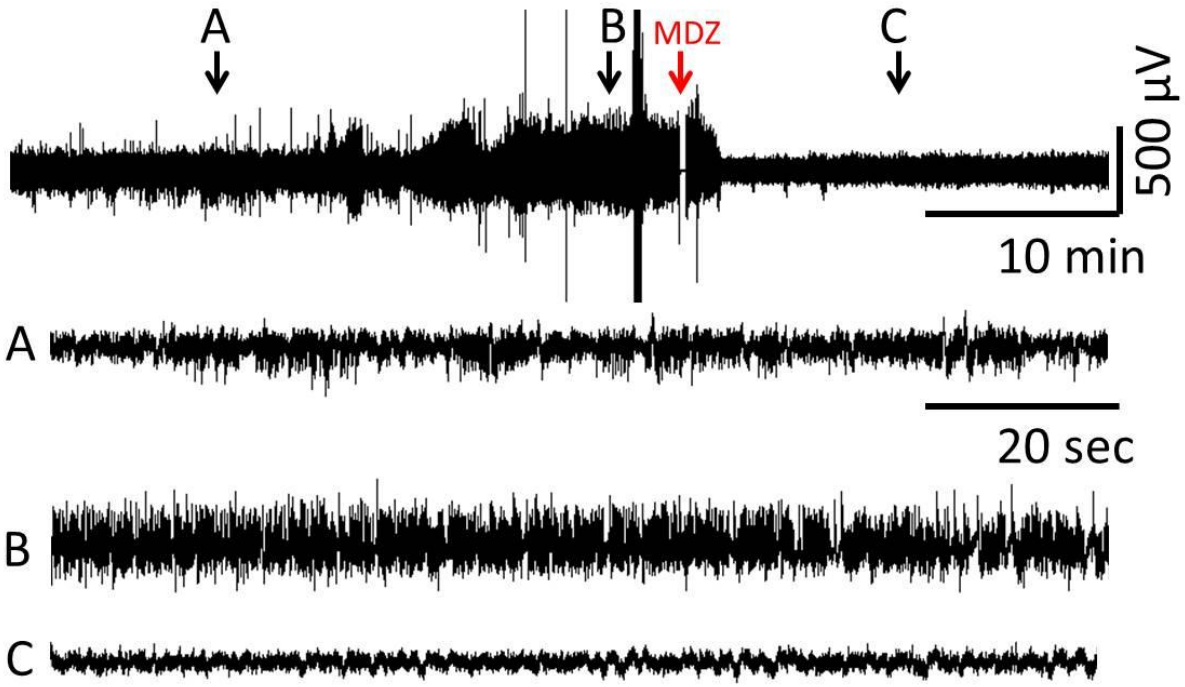

Figure 14. Efficacy of midazolam on SE in rat pups at P21. A and B show an expanded time scale of the activity during SE, C shows the EEG trace after 2 mg/kg midazolam (i.p.).

A non-linear mixed-effects analysis of SE in P21 rats treated with vehicle or 2 mg/kg midazolam 1 hr after administration of DFP showed a decrease in power in the gamma band in the MDZ-treated animals compared to the animals which received vehicle only (Fig. 15). This analysis confirmed the rapid decrease of activity in the gamma band after midazolam, and demonstrates that 2 mg/kg MDZ is efficacious in ameliorating SE at this age. A similar effect on electrographic SE was observed for 10 mg/kg diazepam (Fig. 16).

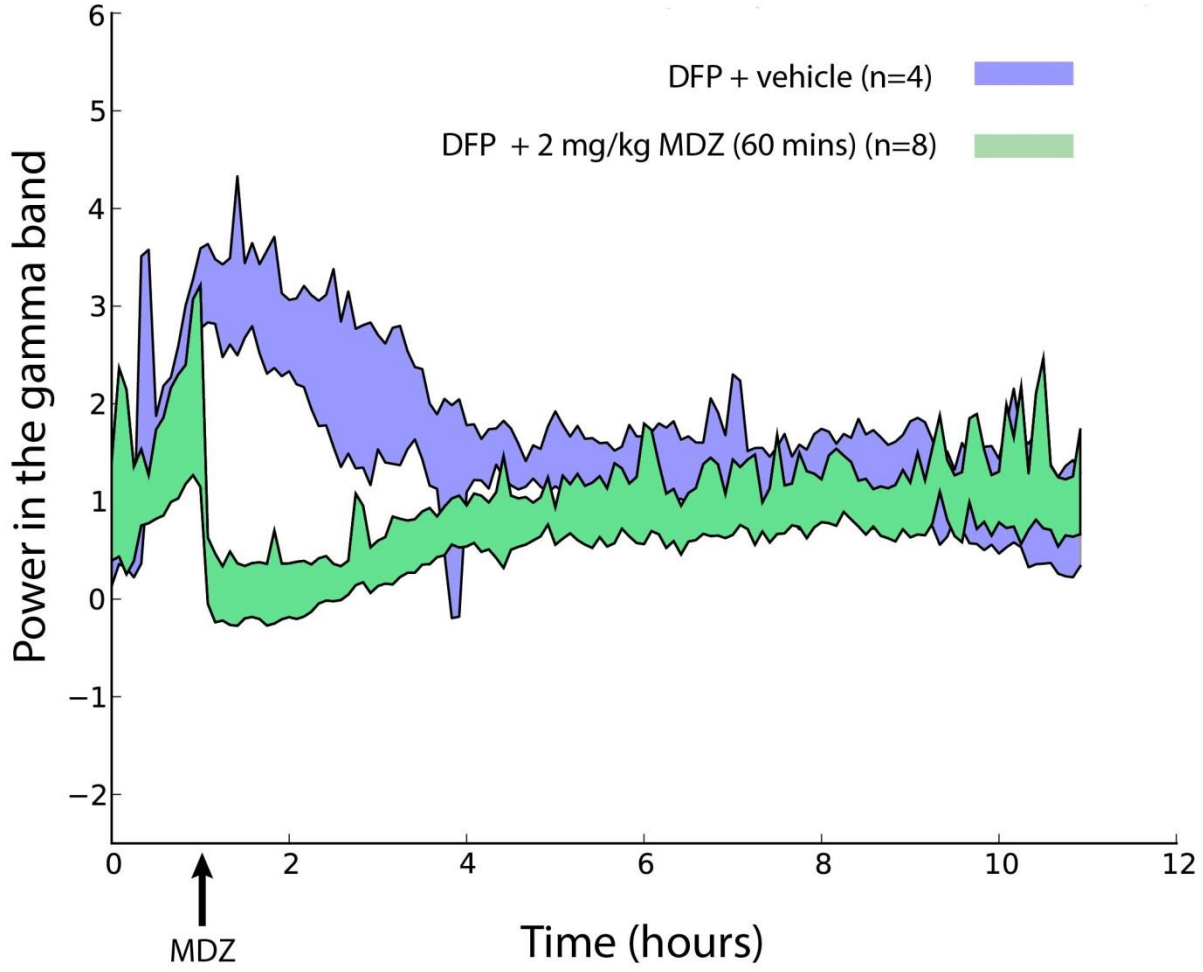

Figure 15. Change in power in the gamma band (20–70 Hz) plotted with 95% confidence limits over the 10 hr period after treatment with DFP in rat pups at P21 for vehicle (blue trace) or 2 mg/kg midazolam (green trace).

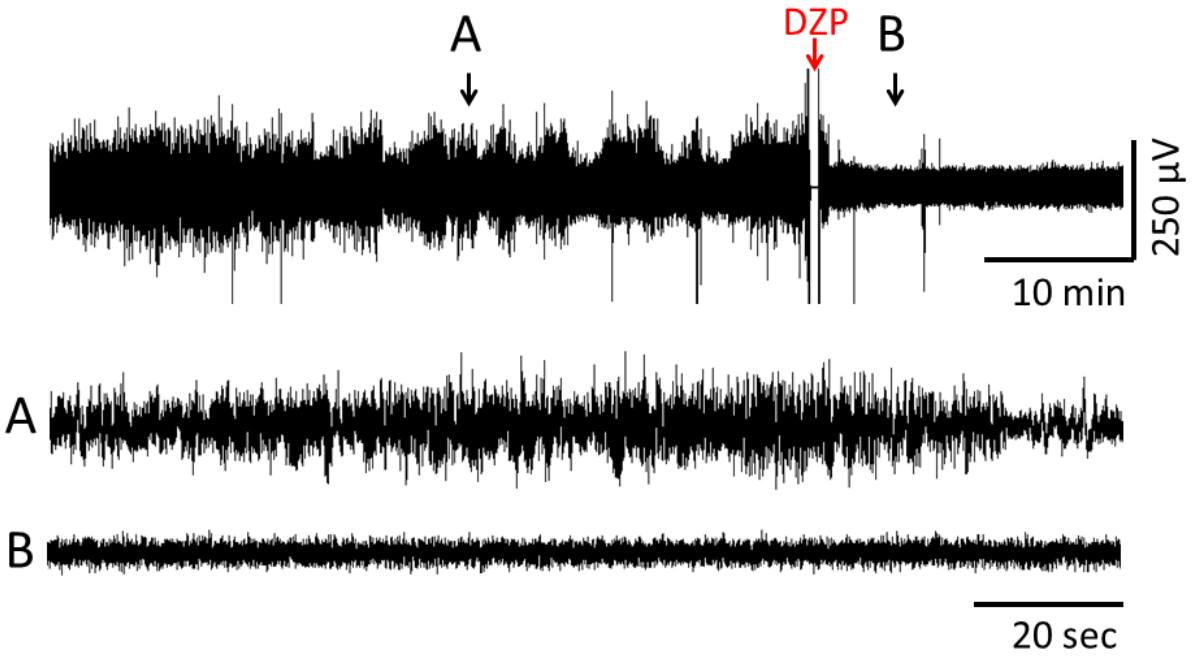

Figure 16. Efficacy of diazepam on SE in a P21 rat. A represents an expanded time scale for record during SE, B shows the EEG trace after 10 mg/kg diazepam (DZP) was given i.p.

Effect of midazolam on neuronal death assayed with F-J B

Twelve regions of brain from Bregma -2.3 through -6.3 were studied in drug- and vehicle-treated rat pups at P21>the animals were euthanized 1 hr after seizures. In Table 3, the yellow highlighting indicates statistically significant differences between drug- and vehicle-treatment. As shown in Table 3 and Figure 17, more regions of interest were protected by midazolam than by diazepam at these drug concentrations. Both MDZ and DZP provided neuroprotection to the dCA1 region, but only MDZ showed a decrease in the number of F-J B-positive neurons in MD and Pir. Evidence of neurodegeneration occurred only in animals that sustained both behavioral and electrographic SE; animals that displayed only behavioral seizures had no F-J B staining.

Table 3. Average ± SEM, P21 DFP-treated rat pups treated with vehicle, midazolam (MDZ) or diazepam (DZP) 60 min following DFP. Abbreviations: dCA1, dorsal CA1; dCA3, dorsal CA3; DG, dentate gyrus; BA, basolateral amygdala; LA, lateral amygdala; MD, mediodorsal thalamic nucleus; Pir, piriform cortex; ENT, entorhinal cortex; vCA1, ventral CA1; vCA3, ventral CA3. All abbreviations from Paxinos and Watson (1986).

	Vehicle	2 mg/kg MDZ	10 mg/kg DZP
dCA1	*2.21 ± 0.33*	*1.02 ± 0.10***	*1.15 ± 0.36**
dCA3	0.68 ± 0.11	0.25 ± 0.12	0.54 ± 0.15
Hilus	0.41 ± 0.13	0.03 ± 0.02	0.56 ± 0.21
DG	1.34 ± 0.25	1.55 ± 0.24	1.42 ± 0.11
BA	*2.51 ± 0.06*	*1.92 ± 0.19**	*2.17 ± 0.06***
LA	2.35 ± 0.09	2.15 ± 0.23	2.40 ± 0.14
MD	*2.57 ± 0.08*	*1.84 ±0.16**	*2.44 ± 0.15*
Pir	*2.89 ± 0.09*	*2.02 ± 0.27**	*2.70 ± 0.16*
Par	0.79 ± 0.35	0.04 ± 0.02	0.10 ± 0.10
ENT	*2.95 ± 0.04*	*1.56 ± 0.19****	*2.41 ± 0.18**
vCA1	2.21 ± 0.31	1.31 ± 0.33	1.25 ± 0.47
vCA3	0.48 ± 0.10	0.36 ± 0.18	0.41 ± 0.16

*p < 0.05, **p < 0.01, and ***p < 0.001 compared to vehicle
One way ANOVA with two-tailed t test with selected pairs. Bonferroni post-hoc test.
Vehicle: n = 11; MDZ: n = 7; DZP: n = 7

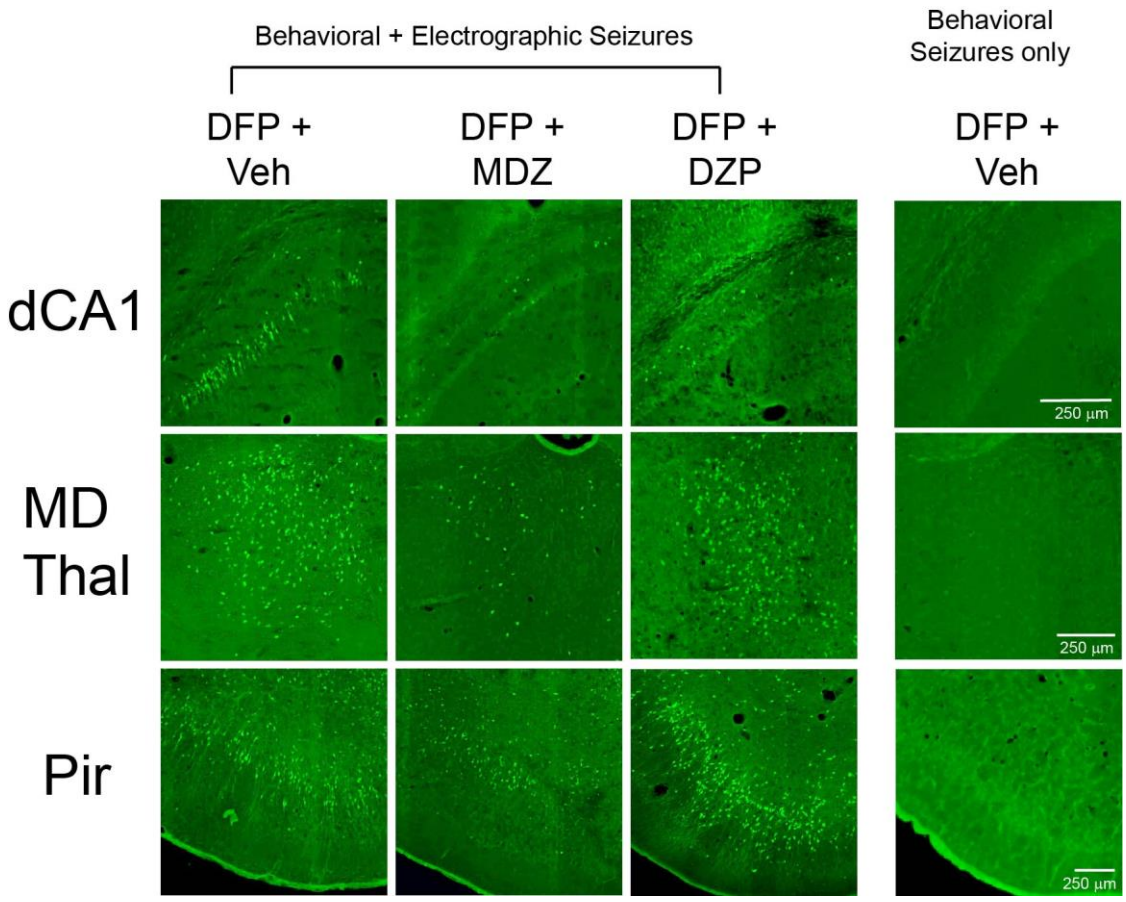

Figure 16. Examples of Fluoro Jade-B labeled brains of P21 rat pups 24 hr after DFP exposure. MDZ, 2 mg/kg midazolam ; DZP, 10 mg/kg diazepam.

Key Research Accomplishments

- Provided investigators at the USAMRICD with the miniature telemetry system
- Established behavior of P7, P14, P21, and P28 animals in response to DFP
- Developed model of OP (DFP) in telemetry-implanted P7, P14, P21, and P28 rat pups
- Analyzed EEG of DFP-treated immature rats
- Examined neuropathology of DFP-treated immature rats using Fluoro-Jade B
- Assessed the effect of midazolam and diazepam in DFP-treated rats at P21

Reportable Outcomes

Absracts and posters

Scholl, EA, Lehmkuhle, M., McDonough, J, Dudek, FE. A Pediatric Model of Organophosphate-Induced Status Epilepticus in Freely Moving Juvenile Rats. Poster: Society of Toxicology meeting in San Antonio, TX, March 10-14, 2013.

Miller, SM, Scholl, EA, McDonough, J, and Dudek, FE. Development of Rodent Models of Childhood Seizures After Exposure to Organophosphates or Nerve Agents. Poster: CounterACT meeting, Bethesda, MD, June 25-27, 2013.

Miller, SM, Scholl, EA, McDonough, J, and Dudek, FE. Evaluation of anticonvulsants to treat nerve agent- and pesticide-induced seizures and prevent brain damage in pediatric rats. Poster: CounterACT meeting, Denver, CO, June 17-19, 2014.

Scholl, EA, Simon, N, Lehmkuhle, MJ, Roper, P, Ekstrand, JJ, Dudek, FE. Lithium pilocarpine and DFP-induced status epilepticus in immature rats: behavioral, electrographic, and neuropathological characteristics. Poster: American Epilepsy Society meeting, Seattle, WA, December 5-9, 2014.

Manuscript in preparation

Scholl, EA, Miller, SM, Lehmkuhle, MJ, Ekstrand, JJ, Dudek, FE, McDonough, J. Rodent models of childhood seizures after exposure to organophosphates or nerve agents.

Conclusion

Electrographic SE and seizures, in addition to seizure-like behaviors, were studied in rat pups at ages postnatal day 7 to 28 (P7-P28) in response to an organophosphate (DFP); the effects of DFP were compared to those observed in response to the cholinomimetic, lithium pilocarpine (Li-Pilo). Behavior was not coupled to electrographic seizure activity, thus emphasizing the need for the use of instrumented animals in analyses of evoked seizures in the immature brain. P7 rat pups sometimes showed electrographic seizure activity in response to LiPilo, but rarely to DFP. After either DFP or LiPilo treatment, P14 rat pups showed electrographic SE, although the duration of the repetitive seizures was shorter than observed at P21 and P28. Initial studies with Fluoro-Jade B showed extensive injury in DFP- and LiPilo-treated rats at P28 and P21 rats, particularly in the hippocampus, thalamus, and amygdala. Pharmacological evaluation of midazolam and diazepam in DFP-treated rat pups at P21 indicated that both midazolam and diazepam were efficacious in halting both electrographic and behavioral SE, although midazolam showed increased neuroprotection over diazepam at the doses tested. Because only rat pups in the P21-P28 age range exhibited robust electrographic SE with both DFP and LiPilo, only these two age groups are presently ready for studies concerning the effects of investigational compounds on repetitive seizures and neuronal death. Additional studies are underway to optimize the animal model at younger ages.

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